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Research Article

Evaluation of efficacy and safety of oral olmesartan + chlorthalidone combination in the management of hypertension in Indian patients

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ABSTRACT

Background: Hypertension is a major health problem in India. Being a multifactorial condition often requires the administration of multiple drugs. Despite improvements in the management of hypertension and the availability of effective antihypertensive agents, only 50% of these individuals achieve BP control. The present study was undertaken to evaluate the efficacy and safety of, fixed dose combination of olmesartan 40 mg + chlorthalidone 12.5 mg, in the management of hypertension uncontrolled with olmesartan monotherapy.
Methods: 110 patients were enrolled in this Post-Marketing Surveillance (PMS) study. Patients were prescribed to take fixed dose combination for 60 days.
Results: There was significant decrease (P <0.0001) in Systolic Blood Pressure (SBP) & Diastolic Blood Pressure (DBP) from the baseline to 15th, 30th and 60th days of the treatment. At the end of the study period of 60 days 95.4% & 90.9% patients of age group >60 years and <60 years achieved the Joint National Committee (JNC VIII) recommended goal respectively. (<150/90 for elder patients aged above 60 year and 140/90 for those aged less than 60 years).
Conclusion: Thus fixed dose combination therapy of olmesartan & chlorthalidone has been shown to be excellent in efficacy and tolerability & gives another option for the optimal management of hypertension.

Keywords: Diastolic, Systolic, Blood pressure, Hypertension, Fixed dose combination, Target goal, Uncontrolled hypertension

INTRODUCTION

An achievement of recommended goal of target Blood Pressure (BP) [<150/90 mmHg in elderly >60 years hypertensive, <140/90 mm Hg in hypertensives with Diabetes Mellitus (DM)], CKD (Chronic kidney disease) is difficult in majority of patients with hypertension.[1,2]

In developed and developing countries, uncontrolled BP remains a major public healthcare problem. Untreated hypertension leads to progressive rise in blood pressure, and often gives resistant state due to associated vascular and renal damage.[3]

It is a major risk factor for stroke (ischaemic and haemorrhagic), myocardial infarction, heart failure, chronic kidney disease, peripheral vascular disease, cognitive decline and premature death.[4]

Hypertension acts synergistically with diabetes and dyslipidemia; can coexist frequently in increasing the risk of both macrovascular and microvascular complications.[5]

Hence, BP control has been found to be difficult to achieve with monotherapy.[6]

National Health and Nutrition Examination Survey (NHANES III) has shown that 64% of patients with hypertension also have dyslipidemia and conversely, approximately 47% of patients with dyslipidemia have hypertension. Hypertension and hypercholesterolemia are the two leading risk factors for heart disease; these two together cause an increase in coronary heart disease related events.[7]

Various studies have shown that tight control of BP is required to produce the maximum reduction in clinical cardiovascular end points.[8,9]

In India, the situation is more alerting as hypertension contributes for nearly 10% of all deaths. Prevalence of hypertension in India is reported to vary from 4-15% in urban and 2-8% in rural population.[10]

It is estimated that the worldwide prevalence of hypertension would increase from 26.4% in 2000 to 29.2% in 2025.[11]

The European Society of Hypertension and Cardiology, states that the primary goal of treatment is to achieve the maximum reduction in long-term total risk of cardiovascular morbidity and mortality.[12]

BP with single agent that acts through one particular mechanism may be unrealistic. Combining the second agent may lead to better control, acting by complimentary mechanism.

Recent epidemiological studies indicate that the approach of using monotherapy for the control of hypertension is not to be successful in most patients and especially in those with some co morbidities (e.g. DM, heart failure).[13,14]

The achievement of BP goal typically require 2 or more medications in single-pill Fixed-Dose Combination (FDC) products because more than 50% will require more than one drug for appropriate control of their BP.[15]

Combination of drugs make them available in a convenient dosing form, lowers the dose and can be given in once daily schedule thus improving patient compliance.

Combination of drugs leads to an additive or synergistic antihypertensive effect at lower doses of individual components and at the same time the drugs in combination counteract the side effects of each other. This helps more patients to achieve normal BP and even can be effective in hard-to treat populations.

Early normalization of BP may greatly motivate the patients to adhere to lifelong treatment.[16]

Monotherapy achieves only a limited number of patients target goal of BP. Since hypertension is multifactorial disease, most patients require two or more antihypertensive agents with different mechanisms of action for the optimal management.[12,17]

This approach is also recommended by the Joint National Committee (JNC VIII) on prevention, detection, evaluation, and Treatment of High Blood Pressure.

METHODS

This study was a post marketing, non-randomized, open, non-comparative, multi centric study. The fixed dose combination of olmesartan 40 mg and chlorthalidone 12.5 mg was administered to hypertensive patients once daily for 2 months (60 days). Informed consent was taken from the patients & the post marketing surveillance was in accordance with the principles in declaration of Helsinki and Good Clinical Practice (GCP).

Inclusion criteria

Both male and female hypertensive patients aged >25 years old with seated cuff ≥160 mmHg and DBP ≥100 mmHg and who were willing to give informed consent were included.

Exclusion criteria

Patients with any condition which in the opinion of the investigator makes the patient unsuitable for inclusion like; known or suspected secondary hypertension, history of asthma or angina, female patient who was pregnant or to get pregnant and patients with known hypersensitivity to any of the ingredient of the fixed dose combination were excluded from the study.

Patient distribution

Out of 110 patients 47 were female and 63 were male patients in the age range of 25-92 years old (Table 1).

Efficacy and safety evaluations

To evaluate the efficacy following parameters were observed.

Primary outcome measures: Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP) were included in primary outcome, which were evaluated at 15th, 30th and 60th day of treatment.

Secondary outcome measures: Global assessment of efficacy and safety were included in this outcome & patients achieving the goal set by JNC VIII that is <150/90 for elder patients aged above 60 year and 140/90 for those aged less than 60 years with or without diabetes.

Global assessment regarding safety was evaluated by recording any adverse event or any complaint during the therapy during every visit. Safety outcomes include mainly symptoms related to hypotension like blurred vision, confusion, dizziness, nausea, vomiting, weakness or any other untoward effects. Patients were interviewed and asked about the type of adverse events throughout the study.

Statistical analysis

Data analysis on patient demographics and various outcome measures were performed using graph pad prism 6. Comparison between the baseline values with the value on the 15th, 30th and 60th day of treatment were made, as well as comparison in between these days were made by applying one way analysis of variance & the Turkeys multiple comparison test. Value of P <0.05 were considered as significant.

RESULTS

SBP and DBP were recorded. In addition, overall efficacy and tolerability was assessed at the end of the study period. The baseline characteristics of patients are summarized in the Table 1.

Table 1: Baseline characteristics of all patients.

Baseline characteristics	
Male/female (n)	63/47
Age (years) range	25-92
Number of patients >60 years	22
Number of patients <60 years	88
SBP (Mean ± SD) mmHg	165.8 ± 15.03
DBP (Mean ± SD) mmHg	97.9 ± 7.28

Systolic blood pressure (SBP)

The SBP was measured at base line and then subsequently at 15th, 30th and 60th days of treatment. The baseline SBP (Mean ± SD) was 165.8 ± 15.03 mmHg. The mean SBP at 15th, 30th and 60th days of treatment were 156.2 ± 13.13 mmHg, 148.2 ± 10.98 mmHg and 138.6 ± 7.17 mmHg respectively. There was statistically highly significant (P <0.0001) decrease in SBP from the baseline to the 15th, 30th and 60th day of treatment (Table 2, Figure 1).

SBP decreased by -9.60 ± 1.9 mmHg, -17.60 ± 4.05 mmHg and -27.20 ± 7.86 mmHg from the baseline to 15th, 30th and 60th day of treatment respectively. (Table 3, Figure 3).

Table 2: Effect of drug therapy on BP.

	Baseline	Day 15***	Day 30***$^{\#}$	Day 60***$^{\#}$
Mean ± SD mmHg (SBP)	165.8 ± 15.03	156.2 ± 13.13	148.2 ± 10.98	138.6 ± 7.17
Mean ± SD mmHg (DBP)	97.93 ± 7.28	88.65 ± 5.41	84.76 ± 4.91	80.80 ± 4.22

***P <0.0001 vs. baseline, #P <0.0001 vs. Day 15

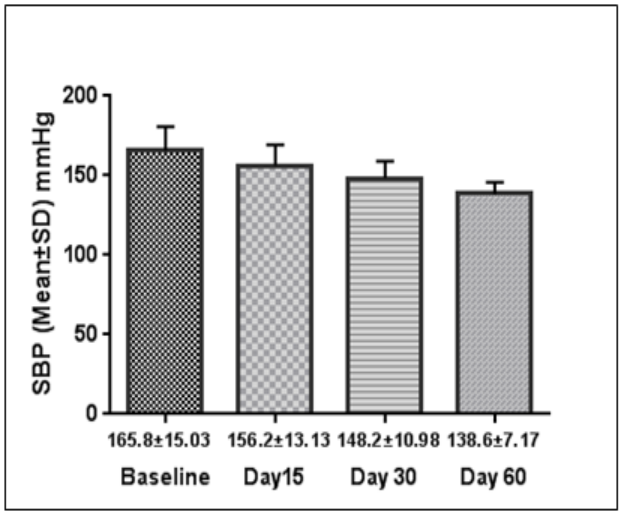

Figure 1: Systolic blood pressure.

Diastolic blood pressure (DBP)

The DBP was measured at base line and then subsequently at 15th, 30th and 60th days of treatment. The baseline DBP (Mean ± SD) was 97.93 ± 7.28 mmHg. The mean DBP at 15th, 30th and 60th days of treatment were 88.65 ± 5.41 mmHg, 84.76 ± 4.91 mmHg and 80.80 ± 4.22 mmHg respectively.

There was statistically highly significant (P <0.0001) decrease in DBP from the baseline to the 15th, 30th and 60th day of treatment (Table 2, Figure 2).

DBP decreased by -9.28 ± 1.87 mmHg, -13.17 ± 2.37 mmHg and -17.13 ± 3.06 mmHg from the baseline to 15th, 30th and 60th day of treatment respectively (Table 3, Figure 3).

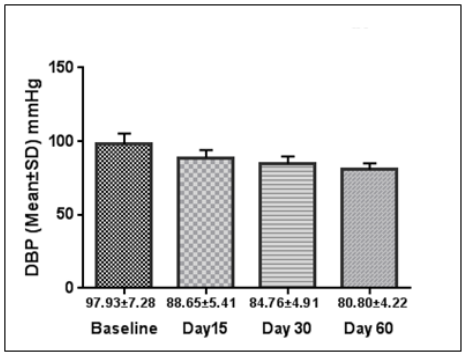

Figure 2: Diastolic blood pressure.

Table 3: Change in SBP and DBP from the baseline (Mean ± SD mmHg).

BP	Day 15	Day 30	Day 60
ΔSBP	-9.60 ± 1.9	-17.60 ± 4.05	-27.20 ± 7.86
ΔDBP	-9.28 ± 1.87	-13.17 ± 2.37	-17.13 ± 3.06

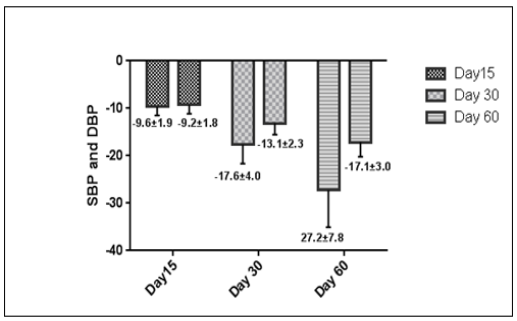

Figure 3: Change in SBP and DBP from the baseline (Mean ± SD mmHg).

Achievement of JNC VIII goal

As per JNC VIII recommended target goal for patients >60 years old is 150/90 mmHg and 140/90 mmHg for patients of age <60 years. During and after the treatment following are the percentage of patients achieving the target BP goal (Table 4).

Table 4: Percentage of patients (>60 years and <60 years) achieving the target BP respectively <150/90 mmHg and <140/90 mmHg.

	Day 15	Day 30	Day 60
% of patients (n) >60 years	(09/22) 40.9%	(18/22) 81.8%	(21/22) 95.4%
% of patients (n) <60 years	(06/88) 06.8%	(26/88) 29.5%	(80/88) 90.9%

Global assessment of safety

Treatment was well tolerated and 13 out of 110 patients (11.8 %) complained about the side effects like general weakness, headache and dizziness.

DISCUSSION

The economic burden of Hypertension is significant for health care resources in terms of the cost of medications and physician visits. It is primarily because of CV morbidity, including coronary heart and cerebrovascular diseases, and consequently economic due to the costs of managing cardiovascular events.[18]

There are no published studies of olmesartan in combination with chlorthalidone in Indian patients & the present study is the first to evaluate the efficacy and safety in Indian patients.

Treatment adherence is an important issue for a chronic disease such as hypertension, with improvements in adherence expected to result in better long-term clinical outcomes, including reduced CV and renal morbidity/mortality and, consequently, containment of health care costs.[19]

The prevalence of hypertension is increasing from last one decade hence appropriate antihypertensive drug therapy is important.[20]

European guidelines and many other guidelines suggest the need of fixed dose combination therapy for the treatment of hypertension.[17,21] Clinical studies have shown that using fixed dose combinations in a single pill helps in improving the control of hypertension and are efficient to achieve target goal of BP with no safety issues.[22,23]

Combination has synergistic and complementary mechanism of action and higher efficacy compared to monotherapy.[21]

Side effects were mild in nature and did not require discontinuation of therapy. Overall no safety concern for treatment was identified.

At the end of the study period of 60 days 95.4% patients of age group >60 years and 90.9% patients of age group <60 years achieved the Joint National Committee (JNC VIII) recommended goal.

CONCLUSION

Fixed dose combination therapy of olmesartan and chlorthalidone is an effective, safe and convenient treatment approach in controlling the blood pressure and achieving the desired blood pressure goal according to JNC VIII in Indian patients.

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